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# Efficacy and Safety of Continuous Infusion of Mononine® During Five Surgical Procedures in Three Hemophilic Patients

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**We report here five surgeries successfully performed with a continuous infusion of Mononine® (Armour Pharmaceutical Company, Kankakee, IL) in three hemophilic B patients. Before surgery the patients received a bolus dose of 40 to 100 U/kg according to the type of surgery. This injection was followed by a continuous infusion of Mononine®, with an infusion rate of 3.5–7 U/kg/hr in order to maintain a factor IX level between 50 and 100% during the whole surgery and the following 6 days. The infusion rate was further adjusted according to the type of surgery until hospital discharge. This method appears to be safe and efficient, since no abnormal bleeding occurred during surgery and none of the patients presented any thrombotic complication. However, this alternative to intermittent administration of factor IX should be standardized and precisely evaluated, regarding the level and the amount of factor IX required, and the cost of the infused material. In our hands, this cost was decreased by 30–40% compared to previous therapeutic schedules at our institution. Am. J. Hematol. 58:110–116, 1998.**


**Key words: continuous infusion; surgery; hemophilia B; factor IX**

## INTRODUCTION

The prevention of bleeding complications that can occur during or after surgery in hemophilic patients is based upon the infusion of anti-hemophilic factors. This substitution is usually realized with repeated injections every 8 to 12 hr. However, this type of treatment presents several disadvantages, i.e., large variations of the anti-hemophilic factor level in the plasma, difficulties reaching a stable plasma level, repeated nursing cares, with the inherent risks of nosocomial infections or dosage errors.

The continuous infusion of antihemophilic factor is a potentially interesting therapeutic alternative since it avoids the peaks of coagulant factor that are generated with intermittent injections. Moreover, the biological control of the plasma level of the coagulant factor may be performed at any time during therapy. Finally, the quantity of anti-hemophilic factor needed is considered to be approximately lowered by 30% [1].

The first study of factor VIII continuous infusion was realized in 1970 by McMillan et al. [2] who reported the use of cryoprecipitates in 5 hemophilic A patients during surgery. Further studies using immunopurified or recombinant factor VIII confirmed the advantages of this method compared to bolus injections [3–11].

The infusion of prothrombin complex concentrates (PCC) usually provokes an activation of the coagulation system, and therefore this material is not used for continuous administration. The presence of small quantities of activated coagulation factors [12], or procoagulant phospholipids [13], and a local activation of factor IX [14] have been proposed for explaining this phenomenon. Several thrombotic events have been reported in the literature [15–18] following the administration factor

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IX concentrates, and PCC are commonly administered as discontinuous treatments.

Mononine®, which contains mainly factor IX, but no other activated factors, appears to be one of the less thrombogenic products [19,20]. However, few studies on factor IX continuous infusion have been reported. In 1993, Kim et al. [21], Kurczynski and Moncino [22], and Goldsmith et al. [23] reported, respectively, one case of hemophilia B patient treated with continuous infusion of Mononine® during surgery. In 1995, Schulman et al. [24] reported on the use of continuous infusion of Mononine® in four patients during surgery and for the treatment of bleeding complications.

We present here five surgeries performed in three hemophilia B patients treated by continuous infusion of Mononine®.

## MATERIALS AND METHODS

### Patients

Patient 1 was a 3-week-old child with a mild hemophilia B (factor IX 7%; normal range 50–100%) who was hospitalized for a pylorotomy. He was the first case of hemophilia in this family, and the FIX defect was discovered after the observation of a prolonged APTT.

Patient 2 was a 62-year-old man with a moderate hemophilia B (factor IX 5%) who concomitantly presented with Osler-Weber-Rendu syndrome implicated along with the hemophilia B in a long history of recurrent epistaxes. He underwent previously multiple dental extractions and a bilateral stripping with intermittent infusions of Mononine®. This patient was admitted for a surgical draining of a post-traumatic hematoma of the right leg.

Patient 3 was a 40-year-old man with a moderate hemophilia B (factor IX 2%) who needed a bilateral knee arthroplasty. He was admitted first for the right knee replacement and 6 months later for the left knee.

None of these patients had a factor IX inhibitor.

### Product

The factor IX concentrate (Mononine®, Armour Pharmaceutical Company, Kankakee, IL) is a concentrate of factor IX prepared from pooled human plasma. Mononine® is purified from plasma proteins by an immunoaffinity chromatography method. A murine monoclonal antibody to Factor IX is used as an affinity ligand to isolate Factor IX from the raw material. Factor IX is then eluted from the monoclonal antibody, further purified, formulated and provided as a sterile, lyophilized powder. The immunoaffinity protocol produces a highly pure Factor IX preparation that shows predominantly a single component on SDS-PAGE evaluation. The specific activity is not less than 150 Factor IX units per mg total protein.

Following the reconstitution of the product as recommended by the manufacturer, each milliliter contains approximately 100 IU of factor IX and non-detectable levels of factors II, VII, and X (<0.0025 U per Factor IX unit, using standard coagulation assays). It also contains 10 mM histidine, 0.066 M sodium chloride, and 3% mannitol. The reconstituted product was immediately transferred into a plastic syringe (polyvinyl chloride) used for continuous infusion.

### Devices and Continuous Infusion

Thirty minutes before surgery, a bolus dose of 40–100 U/kg Mononine® was administered to achieve a plasma factor IX activity of at least 80% for major surgery and 50% for minor surgery. A factor IX continuous infusion was immediately begun using an infusion system: (1) electronic pump, CADD-PCA 5800 (Pharmacia Deltec, St. Paul, MN) with its Medication Cassette-reservoir (also from Pharmacia Deltec) and 76-cm tubing (Pharmacia, St quentin-Yvelines, France); or (2) electronic pump, SE 200 B, (Viale Medical, St Martin le Vinoux, France), with a syringue Luer Lock (Becton Dickinson, Dublin, Ireland), connected to a tubing 155. 20/1.2 mm, L/200 mm (Laboratoire Vygon, Ecoven, France).

The product was administered through a central line for adult patients (1) Cavafix, splittocan 375 (B. Braun, Melsungen, Germany); or (2) Insyte, W.1.3 × 44 mm (Apotecnia Aubagne, France) in order to inject Mononine® in a large vein with a strong flow, avoiding the addition of anticoagulant in the infusion system. The infusion of Mononine® was done through a peripheral access in the 3-week-old patient. The initial infusion rate was 3.5 to 7U/kg/hr, and was able to maintain a factor IX plasma level between 50 and 100%, according to the type of surgery, during the whole surgery and the following 6 days.

The infusion rate was adapted according to the factor IX plasma level, evaluated twice a day for the first 2 days and only once for the remaining days, until discharge.

### Factor IX Assay

The factor IX was measured with a one-stage assay from a standard curve, and the results were corrected according to the data obtained with a commercial standard (Behring AG, Marburg, Germany). The deficient factor IX plasma was from Immuno AG (Vienna, Austria).

All the measures were made in duplicate with a STA machine (Diagnostica Stago, Asnières, France).

## RESULTS

### Patient 1

Hemostatic replacement therapy for the pylorostomy was realized with a Mononine® bolus of 60 U/kg, i.e.,

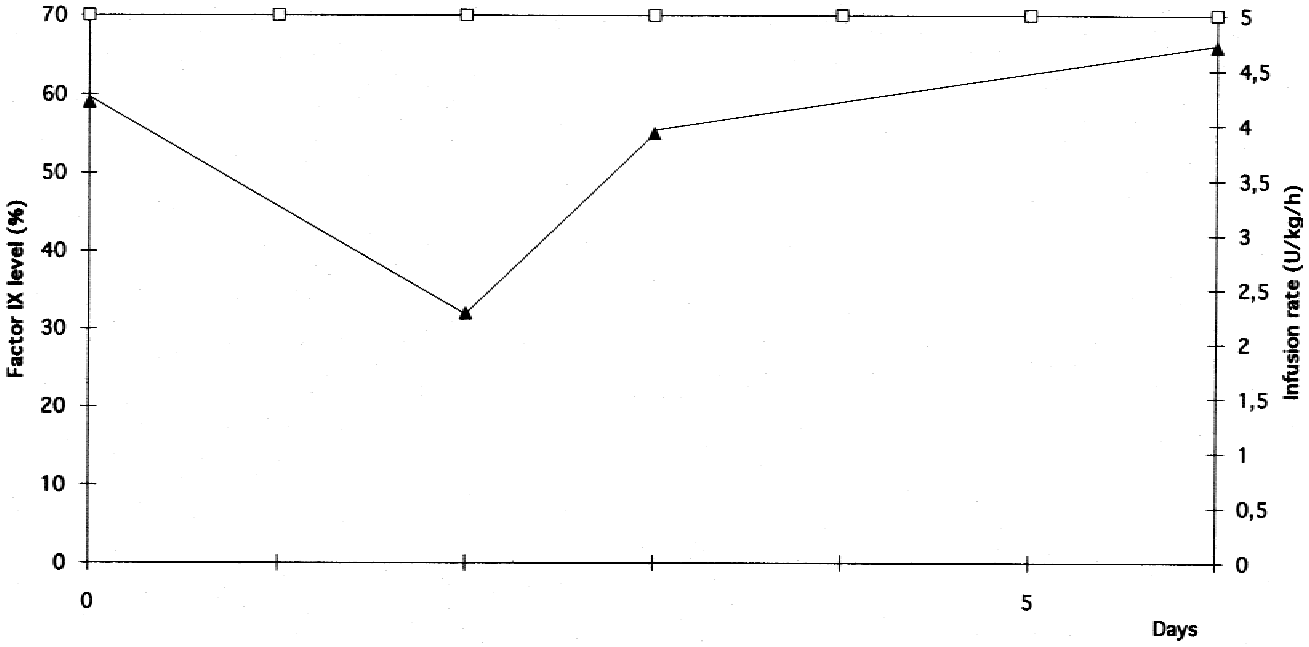


**Fig. 1. Factor IX plasma level (▲) and rate of continuous infusion (□) of Mononine® during a pylorotomy in a 3-week-old minor hemophilia B child.**

500 IU, infused 30 min before surgery. A continuous infusion was immediately started at a dose of 5 U/kg/hr, allowing keeping the factor IX plasma level above 50% during the immediate post-operative period. This infusion rate was maintained during the follow-up at the hospital (Fig. 1) and was sufficient to avoid hemorrhagic complication during or after the surgery. This child was discharged after 7 days with a complete recovery. The total quantity of factor IX infused was 3,600 U.

### Patient 2

In 1994, this patient was admitted for tibial osteotomy due to an abnormal position of the left knee. A bolus of 40 U/kg was injected 4 hr before surgery. Thirty minutes after this injection a continuous infusion was initiated at a rate of 4.8 U/kg/hr. The plasma factor IX level, measured 2 hr later was 48%. A second bolus of 25 U/kg was then injected and the factor IX was found at 62% 4 hr after the end of the surgical procedure. The continuous infusion rate was adjusted during the post-operative period according to the plasma factor IX level, which varied from 40 to 110% (Fig. 2). The blood loss during surgery was 100 ml. During the second and the third day after surgery the bleeding through the drains was 1,000 ml. The hemoglobin level of this patient was 9.5 g/l, due to repetitive epistaxes in the pre-operative period. It rose to 11.5 g/l at the end of the hospitalization. The total quantity of factor IX infused was 78,000 U, during the 17 days of substitution.

Two years later, this patient came back to the hospital for draining a leg hematoma. Fifty units per kg of Mononine® were injected 1 hr before surgery and 30 min after this injection a continuous infusion of Mononine® was started at a rate of 5 U/kg/hr.

During the 9 post-operative days the rate of this continuous infusion varied from 5 to 3 U/kg/hr, allowing maintenance of a factor IX level between 80 and 50%, as presented in Figure 3. The hemoglobin level remained stable and the total quantity of factor IX infused was 66240 U.

### Patient 3

This severe hemophilia B patient was first hospitalized in 1995 for a right knee replacement. Thirty minutes before surgery, a bolus of 100 U/kg was injected, followed by a continuous infusion of Mononine® at 7 U/kg/hr. After surgery, the factor IX level was above 100%, and the continuous infusion rate was maintained. On the first day after surgery, the factor IX level was measured at 144%, and continuous infusion was therefore decreased at 3.5 U/kg/hr. Then, an infusion rate of 2.5 U/kg/hr was used until discharge. The factor IX level was always above 40% (Fig. 4). The blood loss during surgery was 750 ml, and 970 ml was collected through the drains during the post-operative period. The hemoglobin level decreased until 82 g/l on day 2, and further increased until 98 g/l at the end of the hospitalization. The total quantity of infused factor IX infused was 108,640 U during the 22 days of admission.

This patient came back 1 year later for a total left knee replacement. A bolus of 60 U/kg was injected and the continuous infusion was started and kept at 3.5 U/kg/hr

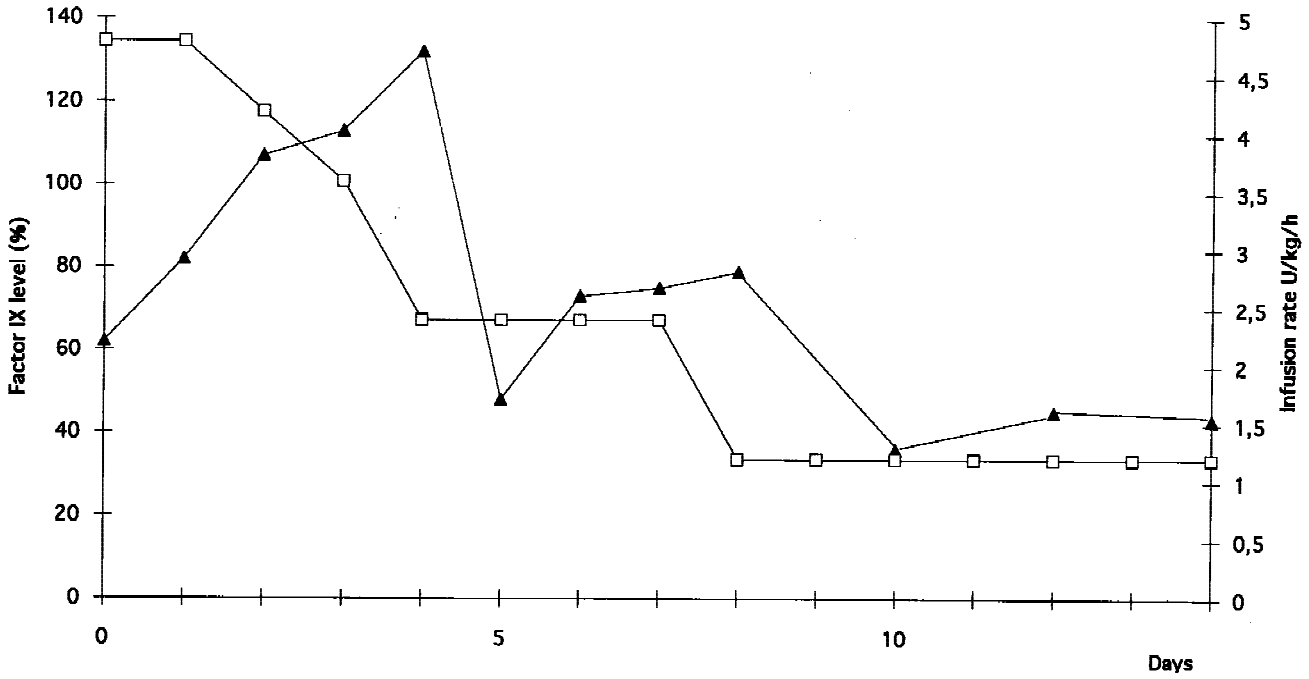


**Fig. 2. Factor IX plasma level (▲) and rate of continuous infusion (□) of Mononine® during a tibial osteotomy of the left knee in a moderate hemophilia B patient.**

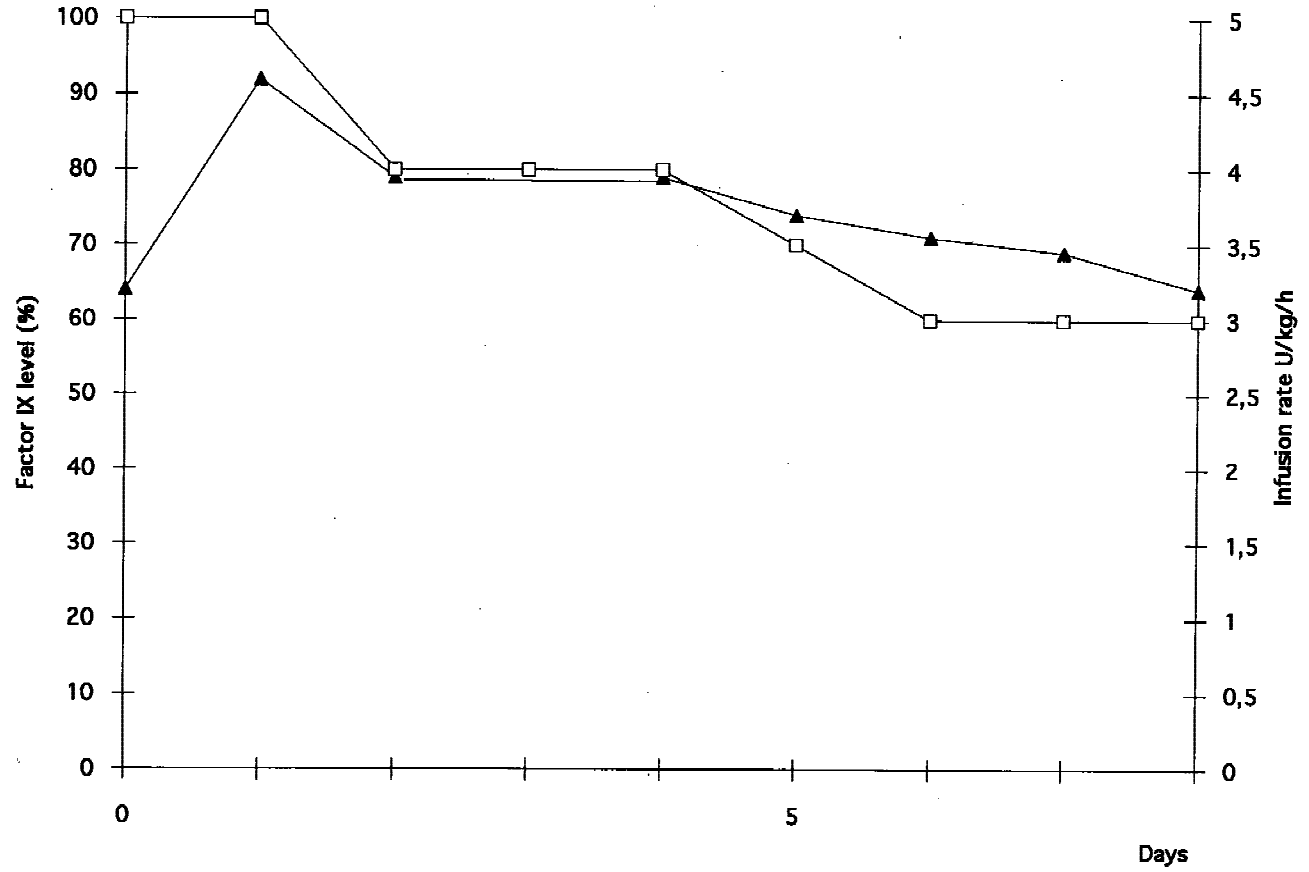


**Fig. 3. Factor IX plasma level (▲) and rate of continuous infusion (□) of Mononine® during an evacuation of a leg hematoma in a moderate hemophilia B patient.**

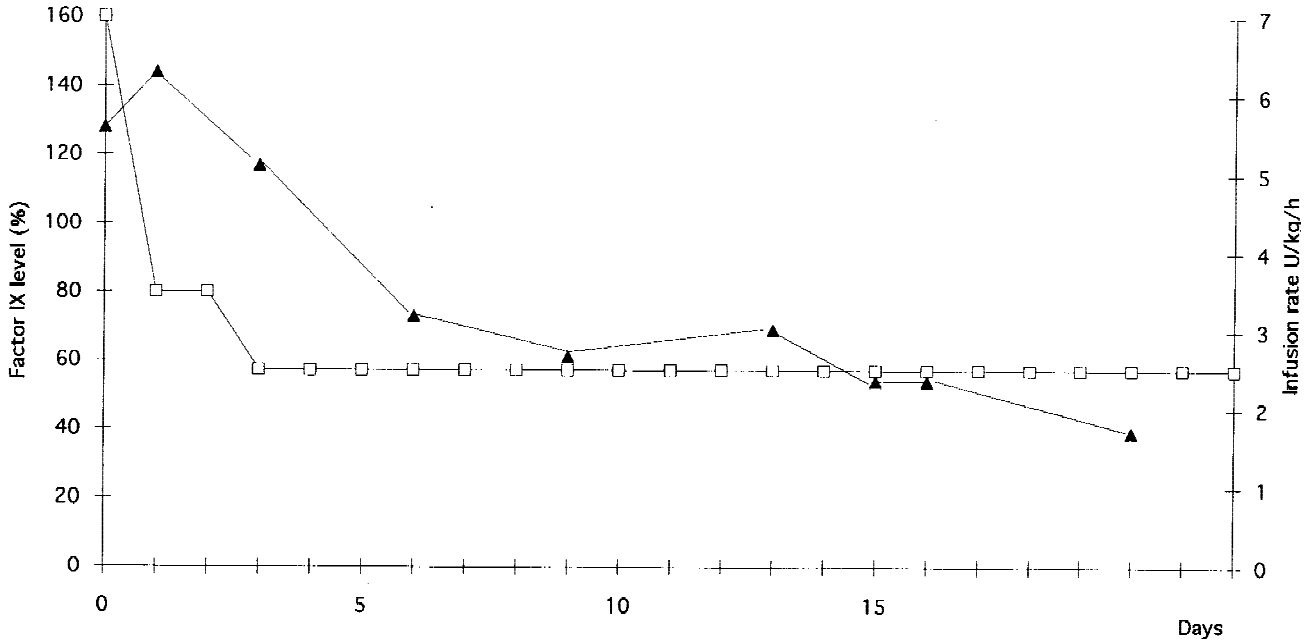


**Fig. 4. Factor IX plasma level (▲) and rate of continuous infusion (□) of Mononine® during a right knee replacement in a severe hemophilia B patient.**

during the first week, maintaining the plasma factor IX level above 60% (Fig. 5). The blood loss during surgery was 800 ml, and 1,000 ml was collected through the drains during the post-operative period. The hemoglobin level remained stable around 90 g/l. The total quantity of factor IX infused was 60,144 U during the 15 days in hospital.

No thrombotic complication was reported during or after these different surgical procedures.

## DISCUSSION

To our knowledge, in addition to the rare reports concerning continuous infusion of Mononine® [21–24], there is little data on continuous infusion of other factor IX concentrates. In 1989, Bona et al. [3] reported the continuous infusion of Konine® (Cutter Pharmaceuticals, Berkeley, CA) in two moderate haemophilia B patients without inhibitors: one of them had been admitted for synovectomy, the other for hemorrhagic syndrome. Stigendal et al. [25] reported the case of a hemophilia B patient who underwent a total hip replacement with a continuous infusion of Immunine (Immuno AG, Vienna, Austria).

Like the other groups, we have not met any technical problem for setting the continuous infusion. Although pharmacokinetic studies prior to surgery would have been proven useful for therapeutic management of these patients, in these instances none were performed. Indeed, in two cases the patients were admitted for emergency situations. Our goal was to maintain a factor IX level above 50% during the first week after surgery and above 30% during the following weeks. The bleeding during and after surgery was considered in the normal range in all cases.

The continuous administration of clotting factor may be considered an efficacious method to deliver the product, and in our experience no bleeding complication was reported. Moreover, neither periphlebitis at the site of injection nor clinical thrombo-embolism occurred during the post-operative period.

Indeed, the main adverse event reported with factor IX concentrates (PCC) containing factor X and II was an abnormal activation of the coagulation cascade. Thus, arterial and venous thromboses were described [15–17]. In a study recently published by Limentani et al. [26], Mononine® was considered to be one of the highest purity products compared with other factor IX concentrates. On a SDS-PAGE analysis (non-reducing conditions), Mononine® showed a single contaminating band compared with products tested that presented multiple contaminating bands. Moreover, factors VII, VIIa, X, II, IIa were not detected in Mononine® by immunoblotting.

Kim et al. [19] did not find any increase of $F_{1+2}$ after an injection of 25 U/kg of Mononine® in hemophilia B patients. Further evidence of a reduced risk of thrombogenicity associated with this immunopurified factor IX was presented by Hadley and Djulbegovic [27], who described the resolution of an abnormal activation of the coagulation cascade with a prothrombin complex concentrate upon substitution with Mononine®.

In a study comparing stability of several factor IX

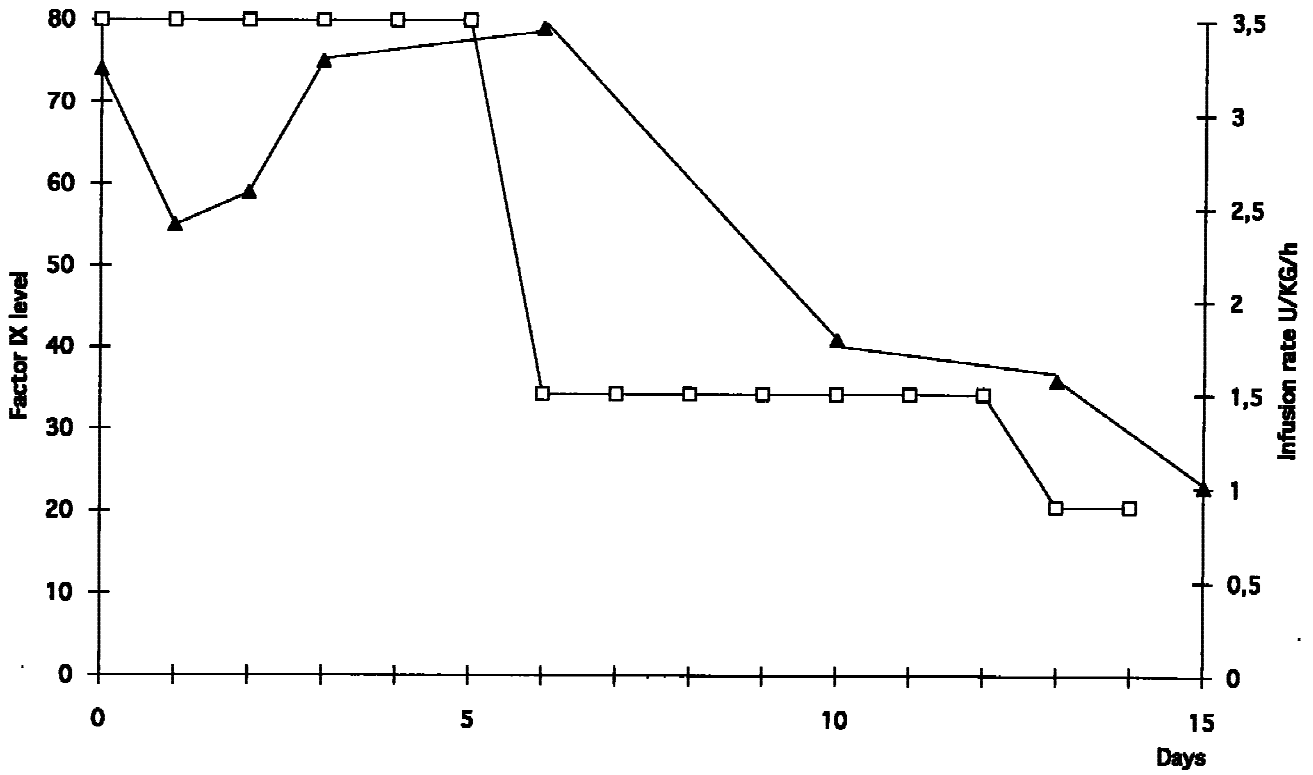


**Fig. 5. Factor IX plasma level (▲) and rate of continuous infusion (□) of Mononine® during a left knee replacement in a severe hemophilia B patient.**

concentrates during continuous infusion, Schulman et al. [24] showed that Mononine® was stable at room temperature during at least 14 days. These results are essential to assure the feasibility and safety of continuous infusion of factor IX concentrates. It might also be suggested that the patient could benefit from a continuous infusion of factor IX during rehabilitation with the use of a portable pump, at least during the first days of physiotherapy.

Our series confirms that continuous infusion of Mononine® is feasible, safe, efficacious, and easy to use. Moreover, the benefits of continuous infusion were very apparent to all members of the multidisciplinary team. Blood samples can be drawn at any time during the postoperative period that could fit with the laboratory practice. The potential risk for nosocomial infection is likely reduced since less preparation steps for reconstituting the product are needed. Continuous infusion saved nursing time, which therefore induces a more efficient organization in the department. Indeed, the time needed for reconstitution and infusion of factor IX two times per day is approximately 1.5- to 2-fold longer than the setting of a continuous infusion of factor IX. Finally, we observed that a lower amount of product was necessary for a correct substitution (between 70 and 60%) compared to bolus injections, as Hathaway et al. [1] pointed out in their study in 1984. This diminution contributes largely to the decrease of the admission cost. However, no consensus has yet been reached on this issue. Since hemophilia B is a relatively rare disease it would, therefore, be interesting to pool national or international hemophilia databases and propose a standardized procedure to the hematologists willing to initiate a continuous infusion at their own institutions.

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